bind to this double-stranded structure as a trimer via Hoogstein (rather than Watson-Crick) base pairing. This is achieved by using an initial population of oligonucleotides (shown in Table 9) having one position that varies between the oligonucleotides, and one degenerate position (N). The oligonucleotides are compared for binding affinity to the target, and the one with the highest binding affinity is selected. Further oligonucleotides are synthesized in which the position occupied by N in the previous round now differs between the oligonucleotides. Comparison of the second round of oligonucleotides, indicates which binds more strongly to the target.

Both the goal of Cook's method and the details of the method steps differ considerably from those of present claim 1. Present claim 1 is directed to methods of analyzing the sequence of a target sequence in which successive estimates of the target sequence are made with successive iterations of the method. By contrast, Cook starts with a target whose sequence is already known (see Fig. 6) and seek to select oligonucleotides that bind to the target sequence. Cook's task is complicated by the fact that he is attempting to isolate oligonucleotide that bind to a double stranded target in trimeric form, in which circumstances normal rules of Watson-Crick pairing do not necessarily apply. Hence, the need for a combination of mutagenesis and selection in Cook's method.

Claim 1 is not anticipated by Cook at least because Cook does not disclose steps of estimating or reestimating a target sequence (steps (d) and (g) in present claim 1). As noted above, Cook starts with a target sequence that is already known and remains unchanged throughout his method. In addition, Cook does not disclose use of both a reference sequence and a target sequence (as specified in steps (a) and (b)) in claim 1. In the present methods, a probe array is designed by complementarity to a known reference sequence, and a target sequence that is a variant of the reference sequence is hybridized to the array. In Cook's method, the same sequence (i.e., the gag pol step shown in Fig. 6) is used both for design of oligonucleotides and for hybridization to the oligonucleotides. Whether this sequence is viewed as being a reference sequence or a target sequence, it cannot be viewed as being both, when one is a variant of the other.

For these reasons, Cook does not anticipate claim 1 and the rejection should be withdrawn.

Claims 1-2 and 5-15 stand rejected as obvious over Cook in view of Cronin. Cook is cited as above. Cronin is cited as teaching overlapping probe sets, use of a reference sequence at least 10 kb long and use of first, second, third and fourth probe sets having interrogation positions, and a target sequence differing from a reference sequence in at least two positions. The Examiner takes the view that it would have been obvious to combine the two references for the benefit noted by Cronin of providing strategies for comparing a reference sequence with a target sequence. This rejection is respectfully traversed.

The rejection applies Cook in the same manner as the anticipation rejection. Accordingly, applicants comments above are equally applicable, and the rejection should be withdrawn for the same reasons.

In addition, it is submitted that the asserted motivation of "providing several strategies for comparing a target sequence with a reference sequence of known sequence" would not have motivated combination of Cronin with Cook. As discussed above, Cook does not compare a reference sequence with a target sequence, but rather uses a strategy of mutation and selection to identify oligonucleotides that binds to a double stranded DNA structure of known sequence. Cooks oligonucleotides are designed specifically with this purpose in mind. As noted above, the probes contain variable and degenerate positions that allow one to narrow down the number of candidate oligonucleotides in successive rounds of the method. It is not at all apparent why a skilled person would replace Cook's own design of oligonucleotides that is specific to his method with an alternate design that is intended for a different purpose, namely, comparing a target and reference sequence.

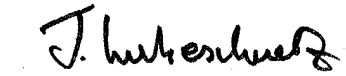
Claims 1-6 and 15 stand rejected as obvious over Cook in view of Horwitz. Cook is applied as above. Horwitz is cited as teaching the identification of homologs of HIV sequences in human and primate DNA. The Examiner takes the view that it would be obvious to combine the comparative human primate study of Horwitz into Cook's method for the benefit of obtaining a better understanding of HIV evolution.

The rejection applies Cook in the same manner as the anticipation rejection. Accordingly, applicants comments above are equally applicable, and the rejection should be withdrawn for the same reasons.

In addition, it is submitted that "the benefit of understanding HIV evolution" would not have motivated combination of the references. The goal of Cook's method is to identify oligonucleotide(s) that bind to a specific known HIV target. This target is used both in the initial design of the oligonucleotides, and in subsequent binding analyses. It is not all apparent how or why the possible existence of homologs of the HIV sequence in other organisms would have any role in this method. For example, if one wishes to isolate oligonucleotides that bind to a HIV viral sequence, it makes most sense to use that sequence both for design of oligonucleotides and in the binding selection steps. This is precisely what Cook does. Use of a homolog sequence for initial design of oligos or screening would seem an unnecessary complication without apparent benefit.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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